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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/077,615	10/23/1998	RAFAEL ARGUELLO	740380CSA	6239

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EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	30

DATE MAILED: 07/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/077,615	Applicant(s) ARGUELLO ET AL.	
	Examiner BJ Forman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-69 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-69 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *25* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response applicant's correspondence submitted 4/5/02, paper number 28. Claims 55, 60, 61, 73, and 76 were amended and claims 70-72 were cancelled. Claims 55-69 and 73-76 are pending and examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

2. The drawings are approved for examination.

Specification

3. This application is in compliance with the sequence rules.

4. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) for the following reasons

(A) Most of the pages of the specification do not have proper margins at the bottom of the page, and a number of these even have text that is cut off (for example, pages 1, 41, and 42). Applicant is reminded that MPEP 601 requires

> "Each sheet must include a top margin of at least 2.0 cm. (3/4 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 2.0 cm. (3/4 inch) and a bottom margin of at least 2.0 cm. (3/4 inch), and no holes should be made in the sheets as submitted. The lines of the specification, and any amendments to the specification, must be 1 ½ or double spaced. The pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers should be centrally located above or, preferably, below the text. See 37 CFR 1.52(b) and MPEP § 608.01."

(B) Page 43 of the specification is missing.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

5. Applicant indicated in the response filed 4/5/02 that a substitute specification was filed therewith. However, the substitute specification was not received. Thus, this requirement is reiterated.

Claim Rejections - 35 USC § 112

6. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the recitation "wherein the database of migration values is independent of the separation" because it is not clear how this is possible. The database of migration values is intrinsically dependent upon the separation as the database is a record of the distances that the test duplexes traveled in the separating step (b). Thus, it is not clear how the database can be independent from the separation. It seems that if the database were independent of the separation, the values contained in the database would be arbitrary values with no clear meaning or basis. For the purposes of examination herein, the claims have been interpreted to mean that the database must be separate from the gel used for separation of the duplexes.

Claim Rejections - 35 USC § 103

7. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517).

This rejection applies to the claims when "exact migration value" is interpreted to require the assignment of a numerical value to the distance traveled by the heteroduplexes.

Zimmerman *et al.* teach a method for identifying an HLA gene comprising:

(a) hybridizing a single strand DNA molecule with a complementary labeled reference DNA strand to form a test duplex (p. 4542, heading "DHDA");

(b) separating the test duplex from at least one control duplex (p. 4542, heading "DHDA"); and

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation (p. 4543 and Fig. 2 and Fig. 3).

(d) assigning a migration value to the position to which the test duplex migrates (see figure 3);

(e) identifying the DNA molecule by matching the migration value with a database of migration values of identified DNA molecules (figures 2 and 3).

(f) repeating steps (a)-(e) one or more times wherein a different allelic strand is used in each repeat to identify the DNA molecule (see figure description for figure 3, the test was run with both DQA1*0102 and DQA1*0501 as the reference probe).

Zimmerman *et al.* use sequence specific oligonucleotide analysis to confirm the identity of the alleles tested (see Figure 3 legend). The method taught by Zimmerman *et al.* can distinguish the second exons of alleles 0102 and 0103, and these differ by only two nucleotides

(see figures 1 and 2). In the methods taught by Zimmerman *et al.* the complementary reference strand and the DNA molecule have the same number of nucleotides, as these are both fragments amplified using the same primers (p. 4542). In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded motilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands." Zimmerman *et al.* teach steps prior to step (a) which include amplifying a DNA molecule to produce double stranded DNA molecules and denaturing the amplified double stranded DNA molecules into single use PCR prior to step (a) (see p. 4542, PCR amplification) and then denature the amplified double stranded DNA molecule into single stranded DNA molecules (see p. 4542, DHDA).

Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the position of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values. With regard to claim 76, the assignment of migration values which are comparative to the control duplex is inherent in the method taught by Zimmerman *et al.* because the determination of the alleles present is a matter of comparison between the reference duplexes and the test duplexes. Thus, the determination of the allele present is a matter of comparing the distance traveled between the reference duplexes and the test duplexes.

Zimmerman *et al.* do not assign an exact numerical migration value to the distance traveled by the heteroduplexes. Furthermore, Zimmerman *et al.* do not provide a database of migration values that is independent of (or separate from) the gel used in the separation step.

Sapirstein *et al.* teach methods which comprise separating proteins from one another and from control proteins, detecting the positions to which the test proteins and the at least one control protein migrates in the separation, assigning an exact numerical migration value to the position to which the test proteins migrates, and identifying the protein pattern by matching the migration value with a database of migration values of protein patterns (p. 492-496). Especially pertinent in this analysis is the fact that Sapirstein *et al.* teach methods for determining band migration distances and relative mobilities of species in an electrophoresis gel and a database for the comparison of such mobility values for the identification of a test sample.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have assigned exact numerical migration values to the movement of heteroduplexes in the methods taught by Zimmerman *et al.*, and to have included these values in a database, as is exemplified by the teachings of Sapirstein *et al.* for a different test system. The ordinary practitioner would have been motivated to do so in order to take advantage of the benefits of database type analysis discussed by Sapirstein *et al.* who teach some benefits of their analysis methodology, including, "Satisfactory precision is obtainable compared to manual measurement procedures using rules or microcomparators...Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern using computer graphics (p. 515)." It would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught

by Zimmerman *et al.* because Zimmerman *et al.* state that the "identifying novel alleles is based on positive detection of HD products with unique electrophoretic mobilities (p. 4545)." Thus the ordinary practitioner would have been motivated to use a measurement method such as the ones taught by Sapirstein *et al.* in order to have provided a clear and quantitative methodology for allele identification.

Zimmerman *et al.* do not teach a method in which the identified DNA molecule is matched to a second identified DNA molecule and the method is used to match tissue between a prospective tissue donor and prospective tissue recipient. However, Zimmerman *et al.* do teach that identifying the molecular diversity within MHC class II molecules has been motivated in large part by the clinical significance of matching donor and host in solid organ and kidney transplants (p. 4541), and that their method provides many advantages over the state of the art SSO-typing methodologies, including a reduced number of probes needed and the ability to use lower stringency conditions, thus eliminating the need for tight control of hybridization and washing conditions, since identification is based o n the detection of HD products with unique electrophoretic mobilities (p. 4545). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method of genotyping taught by Zimmerman *et al.* for tissue donor matching since Zimmerman *et al.* teach the need for typing methods in donor-tissue situations, and Zimmerman *et al.* provide a method with the benefits as discussed.

8. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517), both further in view of Mullins *et al.*

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Mullins *et al.* specifically teach methods in which electrophoresis mobilities are calculated for nucleic acid heteroduplexes (see Example 4). This reference is included in this rejection merely to demonstrate that it was known in the art at the time the invention was made to determine exact numerical mobility values for heteroduplex nucleic acid molecules.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have assigned exact numerical migration values to the movement of heteroduplexes in the methods taught by Zimmerman *et al.* using the methodology provided by Mullins *et al.*, and to have included these values in a database, as is exemplified by the teachings of Sapirstein *et al.* for a different test system. The ordinary practitioner would have been motivated to do so in order to take advantage of the benefits of database type analysis discussed by Sapirstein *et al.* who teach some benefits of their analysis methodology, including, "Satisfactory precision is obtainable compared to manual measurement procedures using rules or microcomparators...Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern using computer graphics (p. 515)." It would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught by Zimmerman *et al.* because Zimmerman *et al.* state

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Response to Remarks

Applicant's remarks concerning the 102 and 103 rejections over Zimmerman *et al.* alone or over Zimmerman *et al.* in view of Mullin *et al.* are moot in light of applicant's amendments to the claims. New grounds of rejection have been provided to address these limitations.

With regard to applicant's arguments concerning the database of values, these arguments have been addressed in the new grounds of rejection. However, it is noted that the examiner's interpretation of Zimmerman *et al.* as providing a "database of values" is within the broadest reasonable interpretation of the claims. Zimmerman *et al.* provide a collection of information organized for comparison, even if this database is in the form of an image of a gel. However, applicant's amendment of the claims appears to be directed at an embodiment in which the database is separate from the gel (as per applicant's arguments), and thus such a database is addressed by the teachings of Sapirstein *et al.*

Conclusion

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C Einsmann
Examiner
Art Unit 1655

June 18, 2002